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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	28

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/973,021	Applicant(s) rsen, Mouritsen, Hindersson, Duch, Sorensen, Da
	Examiner WILLIAM SANDALS	Group Art Unit 1636

X Responsive to communication(s) filed on *Sep 26, 2000*

X This action is **FINAL**.

Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

X Claim(s) *71-117* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

X Claim(s) *71-117* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

X Information Disclosure Statement(s), PTO-1449, Paper No(s). *27*

X Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- *SEE OFFICE ACTION ON THE FOLLOWING PAGES* ---

DETAILED ACTION

Response to Argument

1. All previous claims have been cancelled by amendment in Paper No. 26, filed September 26, 2000, and new claims 71-117 have been entered. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.**

Claim Objections

2. Claims 75, 76, 81 and 84 use the Trademark "PCR". Trademarks are not permitted in claims and must be only referred to by the non-Trademarked concept or composition. Correction is required.

3. Claim 84 is grammatically incorrect at line 2 where it recites "PCR products where are directly introduced". Insertion of "the linear PCR products" between "where" and "are" would correct the problem.

4. Claim 94 is grammatically incorrect at line 1 where it recites "identifies presence". The word "the" should be inserted between "identifies" and "presence".

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 71-117 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claim 71 recites the limitation "said vectors" in line 5. There is insufficient antecedent basis for this limitation in the claim.

8. Claim 71 recites the limitation "said transduced cells" in line 10. There is insufficient antecedent basis for this limitation in the claim.

9. The term "phenotypic trait" in claims 71 and 102 is a relative term which renders the claims indefinite. The term "phenotypic trait" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. A "phenotypic trait" can be **any** trait or characteristic of a cell or organism and the trait or characteristic may have no defined physical, biochemical or biological basis. A "phenotypic trait" may therefore be the same or different trait or characteristic as it may be arbitrarily perceived by an observer, making the term "phenotypic trait" vague and indefinite.

10. Claim 71 recites the limitation "said ribonucleic acid(s) or peptide(s)" in line 13. There is insufficient antecedent basis for this limitation in the claim.

11. Claims 71 and 111 recite the limitation "and/or" in section "e)". This limitation is makes the meaning of the claims unclear, since it not specified whether the preceding limitations apply, or whether the claim may be solely limited to the portion of the claim which follows the "and/or" limitation.

12. Claim 71 recites at lines 26-27 "the ribonucleic acids or peptides containing expression products". It is unclear as to what is meant by this phrase. There may be a step or steps missing to develop the concept that the "ribonucleic acids or peptides" recited at the beginning of line 26 contain expression products. Or it may be that this is a lack of antecedent basis problem. Either way the language must be amended to clarify the meaning of the claim.

13. Claim 71is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting an essential step, such omission does not set forth the method in clear and unambiguous terms. See MPEP § 2172.01. The omitted step is a correlation, or recapitulation step at the end of the claim which restates the preamble.

14. Claim 72 recites the limitation "the peptide" in line 1. There is insufficient antecedent basis for this limitation in the claim.

15. Claim 76 recites the limitation "optimal combining efficiencies of two PCR products" in line 1. There is insufficient antecedent basis for this limitation in the claim.

16. Claim 83 recites the limitation "the viral promoter" in line 2. There is insufficient antecedent basis for this limitation in the claim.

17. Claim 83 recites the limitation "the 5'-LTR" in line 2. There is insufficient antecedent basis for this limitation in the claim.

18. Claim 86 recites the limitation "retroviral packaging cell line viral titer" in line 1. There is insufficient antecedent basis for this limitation in the claim.

19. Claim 89 recites the limitation "the preselected cellular function" in line 2. There is insufficient antecedent basis for this limitation in the claim.

20. Claim 89 rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: a step or steps at line 3 which provide a means for the interaction of "the molecule with which the peptide interacts".

21. The language of claim 91 is unclear and vague. The phrase "linked to a DNA sequence encoding a protein expressed simultaneously" is ambiguous. The term "expressed simultaneously" implys that there is another protein which is also being expressed simultaneously, but the identity of the "other" protein which may be expressed has not been set forth.

22. Claim 94 recites the limitation "the transduced cells" in line 2. There is insufficient antecedent basis for this limitation in the claim.

23. Claim 95 recites the limitation "the preselected cellular function" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

24. Claim 96 recites the limitation "the synthetic totally random DNA sequences" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

25. Claim 97 recites the limitation "the synthetic totally random DNA sequences" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

26. Claim 99 recites the limitation "the synthetic totally random DNA sequences" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

27. Claim 99 recites at line 2 "sequences are separated by codons". The claim appears to lack method steps identifying more than one sequence which may be contained in the viral vector of the base claim. Or, in the alternative, the claim may lack antecedent basis for the claimed sequences.

28. Claim 101 recites the limitation "ribonucleic acid or peptide" in lines 2-3. There is insufficient antecedent basis for this limitation in the claim.

29. Claim 102 recites the limitation "the identical cells" in line 3. There is insufficient antecedent basis for this limitation in the claim.

30. Claim 107 recites the limitation "the synthetic totally random DNA sequences" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

31. Claim 94 is vague and indefinite and appears to lack a method step at lines 1-3 where it recites "synthetic totally random DNA sequences are coupled to coding sequences of purification tags in order to facilitate the purification or expressed peptides". The connection between the encoded purification tags and the necessary expression of the tags for the purification step of the

method has not been established. The word "of" between "coding sequences" and "purification tags" may be substituted by the words "which express" to clarify the fact that the coding sequences need to be expressed "in order to facilitate identification of expressed peptides".

32. The phrase in claim 117, "The method" is indefinite because the word "The" implies that this method has an antecedent basis. The claim is an independent claim, making the use of the word "The" undefined and therefore vague. Deleting "The" and inserting --A-- would cure this defect.

33. The term "which has influence" in claim 117, line 1 is a relative term which renders the claim indefinite. The term "which has influence" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Substitution of the term "which has influence" by a term which is defined in the instant claims and specification is required.

Claim Rejections - 35 USC § 103

34. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

35. Claims 1-18, 20-26, 30 ,31, 37-42, 48, 53 and 59-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 95/04824 et al. (of record) in view of, LaBean et al., Dube et al., WO 94/29469, US Pat No. 5,935,823, Karttunen et al. and Von Melchner et al.

WO 95/04824 taught (see especially the abstract and pages 2, 3, 7, example 6 and example 13) a method of transducing eukaryotic cells with a viral vector which stably integrated into the genome of the cell at one to a few copies per cell, expressing an encoded sequence, which may be totally random sequence, identification of an expressed trait in the cell, selecting said cell, and recovering the DNA sequence encoded by the viral vector. The encoded sequence may then be amplified and sequenced. Packaging cells may be employed to prepare the viral vector for infection of the host cell where the packaging vector may contain gag. The encoded sequence may be fused with or inserted into a sequence which encodes for a protein. The eukaryotic cells may be hematopoietic cells, and the DNA encoded products may be hematopoietic cell receptors.

WO 95/04924 did not teach that the DNA inserts were short sequences which were not genes. Also not taught was a retroviral packaging system with a gag, pol and env sequence provided from the packaging cell line. WO 95/04824 did not teach the random codon synthesis, nor the CMV promoter, nor the identification of T-cell epitopes.

LaBean et al. taught (see the entire article) the general method of generating random sequences encoding random amino acids, and discussed the advantages of introducing random

codons, as well as partially random sequences which reduce or eliminate stop codons in the encoded sequence.

Dube et al. taught (see the entire article) the method of using totally or partially random sequences from a thymidine kinase gene from a herpes viral vector. A bacterial cell was screened for biologically active DNA sequences to identify nucleic acid sequences which encoded unique functions. The encoded DNA was isolated and sequenced, and the encoded RNA and peptides were also sequenced and identified.

US Pat No. 5,935,823 taught (see especially the abstract and the summary and column 21) the method of using viral vectors containing totally random sequences to transform a eukaryotic cell to identify nucleic acid sequences which encoded unique functions. The random sequences of DNA was isolated and sequenced, and the encoded RNA and peptides were also sequenced and identified.

WO 94/29469 taught (see especially page 10, lines 30-32) the equivalence of promoters such as CMV promoters to other well known eukaryotic promoters, such as the viral LTR promoters taught in WO 95/04824.

Karttunen et al. taught (see especially the abstract, introduction and discussion) the well known cloning and identification of T-cell epitopes.

Von Melchner et al. taught (see especially the abstract and the figures) the well known and advantageous use of packaging cells for the production of retroviral vectors which contain

the gag, pol and env genes which vectors are to be used in identifying and characterizing encoded foreign genes contained in the viral vectors.

It would have been obvious to one of ordinary skill in the art at the time of filing the instant application to combine the method of transducing eukaryotic cells with a viral vector which stably integrated into the genome of the cell at one to a few copies per cell, expressing an encoded sequence, which may be totally random sequence, identification of an expressed trait in the cell, selecting said cell, and recovering the DNA sequence encoded by the viral vector. The encoded sequence may then be amplified and sequenced. Packaging cells may be employed to prepare the viral vector for infection of the host cell. The encoded sequence may be fused with or inserted into a sequence which encodes for a protein of WO 95/04824 with the method of generating random sequences encoding random amino acids, and discussed the advantages of introducing random codons, as well as partially random sequences which reduce or eliminate stop codons in the encoded sequence of LaBean et al., and the method of using totally or partially random sequences in a viral vector to transform a eukaryotic cell where the transformed cell was screened for biologically active DNA sequences to identify nucleic acid sequences which encoded unique functions and the encoded DNA was isolated and sequenced, and the encoded RNA and peptides were also sequenced and identified of Dube et al., and the method of using viral vectors containing totally random sequences to transform a eukaryotic cell to identify nucleic acid sequences which encoded unique functions and the encoded DNA was isolated and sequenced, and the encoded RNA and peptides were also sequenced and identified of US Pat No.

5,935,823, and where WO 94/29469, Karttunen et al. and Von Melchner et al. each taught well known adaptations of the methods of eukaryotic transformation and expression for the purpose of identifying the expressed sequences and their respective expressed proteins and peptides because the methods of WO 95/04824 et al., LaBean et al., Dube et al. and WO 94/29469 were each directed to the expression of DNA sequences to identify the expressed sequences and their respective proteins and peptides. The methods of each of WO 95/04824 et al., LaBean et al., Dube et al. and WO 94/29469 taught well known and useful methods of discovery of sequences of DNA and their transcripts and expressed protein and peptide sequences.

One of ordinary skill in the art would have been motivated at the time of filing the instant application to combine the method of transducing eukaryotic cells with a viral vector which stably integrated into the genome of the cell at one to a few copies per cell, expressing an encoded sequence, which may be totally random sequence, identification of an expressed trait in the cell, selecting said cell, and recovering the DNA sequence encoded by the viral vector. The encoded sequence may then be amplified and sequenced. Packaging cells may be employed to prepare the viral vector for infection of the host cell. The encoded sequence may be fused with or inserted into a sequence which encodes for a protein of WO 95/04824 with the method of generating random sequences encoding random amino acids, and discussed the advantages of introducing random codons, as well as partially random sequences which reduce or eliminate stop codons in the encoded sequence of LaBean et al., and the method of using totally or partially random sequences in a viral vector to transform a eukaryotic cell where the transformed cell was

screened for biologically active DNA sequences to identify nucleic acid sequences which encoded unique functions and the encoded DNA was isolated and sequenced, and the encoded RNA and peptides were also sequenced and identified of Dube et al., and the method of using viral vectors containing totally random sequences to transform a eukaryotic cell to identify nucleic acid sequences which encoded unique functions where the encoded DNA was isolated and sequenced, and the encoded RNA and peptides were also sequenced and identified of US Pat No. 5,935,823, and where WO 94/29469, Karttunen et al. and Von Melchner et al. each taught well known adaptations of the methods of eukaryotic transformation and expression for the purpose of identifying the expressed sequences and their respective expressed proteins and peptides because WO 95/04824 taught the use of retroviral vectors containing DNA sequences which may be totally random sequence to transform eukaryotic cells at a low copy number (which may be one copy) per cell to rapidly and efficiently identify sequences which were expressed in the cells, where the sequences expressed RNA and protein or peptides which were recognized by some trait or characteristic, which cells may be hematopoietic cells and the vector DNA may express a hematopoietic cell receptor. LaBean et al. states at the abstract "[l]ibraries of random sequence polypeptides are useful as source of unevolved proteins, novel ligands, and potential lead compounds for the development of vaccines and therapeutics. The expression of small random peptides has been achieved previously using DNA synthesized with equimolar mixtures of nucleotides...Semirandom DNA, synthesized with a designed, three-residue repeat pattern, can encode libraries of very high diversity and represents an important tool for the

construction of random polypeptide libraries." providing excellent motivation to produce random codon synthetic DNA inserts in the vectors of WO 95/04824. Dube et al. at the abstract recites "[s]electing biologically active DNA sequences from large random populations provides a new method for identifying nt [nucleotide] sequences with unique functions." Dube et al. concludes at page 46, column 1, bottom "[i]t seems a reasonable expectation that this method, combined with other methods, collectively referred to as 'applied molecular evolution' will lead to the production of new enzymes and other biological molecules that are entirely different from those present in nature." US Pat No. 5,935,823 taught at column 11, line 49-50, "[]the present invention relates to novel reagents and the process for making them. The invention provides a process for synthesizing and identifying new binding reagents of specific affinity", which is followed at lines 57-58 "[t]he polypeptides or proteins are expressed in prokaryotic or eukaryotic cells as hybrid fusion proteins...", and at column 12, line 66, bridging to the top of column 13 "the first sequence comprises a group of sequences generated by random synthesis....to form a library of vectors expressing fusion proteins...". Karttunen et al. merely provide an exemplary method of producing hematopoietic cell receptors, which are T-cell receptors, which are T-cell epitopes, which are MHC molecules. WO 94/29469 provides well known teachings on the equivalence of eukaryotic promoters such as CMV and LTR, while Von Melchner provides teachings on the well known packaging of retroviral vectors which may include gag, pol and env proteins to facilitate transduction of target cells. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed

invention given the teachings of WO 95/04824 et al. with LaBean et al., Dube et al., WO 94/29469, US Pat No. 5,935,823, Karttunen et al. and Von Melchner et al.

Response to Arguments

36. Arguments set forth in Paper No. 26 assert that WO 95/04824 does not disclose that the encoded sequence may be **totally** random. This is true. However, US Pat No. 5,935,823 provides adequate motivation for one of skill in the art to substitute totally random sequences for the partially random sequences of WO 05/04824 at column 11, lines 52-67 by reciting "Totally Synthetic Affinity Reagents (TSARs) are concatenated heterofunctional polypeptides or proteins....The polypeptides or proteins are expressed in prokaryotic or eukaryotic cells as hybrid fusion proteins comprising at least one binding domain...linked to one or more additional chemically or biologically active effector domains....(which) can include peptide moieties such as an enzyme or fragment thereof, a toxin or fragment thereof, a therapeutic agent, a peptide that is useful for detection, a peptide that enhances expression of the TSAR molecule..." Which is followed at column 12, liness 57-60 "[t]he nucleotide sequence encoding the binding domain of the receptor is mutagenized, using either random, site directed or site selective techniques known to those of skill in the art".

37. Arguments set forth in Paper No. 26 assert that Dube et al. does not teach a method for eukaryotic cells. This is true. However, US Pat No. 5,935,823 provides ample motivation which unites the instant claimed methods employing eukaryotic cells with the prokaryotic methods of Dube et al.

38. Arguments are set forth in Paper No.26 assert that La Bean et al. did not mention libraries useful for transducing eukaryotic cells in order to identify biologically active peptides or RNA. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

39. Arguments set forth in Paper No. 26 assert that US Pat No. 5,935,823 taught the binding of a ligand of choice. This is true, however, the method of US Pat No. 5,935,823 also taught the detection of other types of cellular functions, as set forth in item "36" above.

40. Arguments set forth in Paper No. 26 assert that WO 95/04824 would not lead one to screen for cDNAs and mutants thereof to find new interactions in cells. On the contrary, WO 95/04824 taught in examples 10-13, several examples of finding new interactions in cells.

41. Arguments set forth in Paper No. 26 assert that WO 95/04824 does not teach a method for identification of putative lead compounds in drug development. This is true. However, US Pat No. 5,935,823 taught at column 22, section 5.3 that the use of the totally random synthetic DNAs of the invention may be used in drug discovery.

Arguments set forth in Paper No. 26 assert that the cited references do not teach a method for discovery of unknown sequences, for example, drug discovery. US Pat No. 5,935,823 taught a method for drug discovery of unknown sequences, and each of WO 95/04824 et al., LaBean et al., Dube et al. taught a method for application of random sequences for discovery of the effect

on the target cells. This combination of references provides ample guidance to one of ordinary skill in the art to produce the instant claimed invention.

Conclusion

42. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Friday from 8:30 AM to 5:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott can be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Receptionist, whose telephone number is (703) 308-0196.

William Sandals, Ph.D.
Examiner
December 3, 2000

ROBERT A. SCHWARTZMAN
PRIMARY EXAMINER